Study 20040135:
AE of breast cancer progression (per clinical review)

On treatment phase

	Denosumab	Placebo
	N = 129	N = 120
Disease progression as AE	4 (3.1%)	3 (2.5%)

Off treatment phase (120 day followup)

	Denosumab	Placebo
	N = 93	N = 92
Disease progression as AE	2 (2.1%)	2 (2.2%)

Standardized Incidence Ratios (SIR) for Malignancies of Selected Cancer Types (Denosumab Subjects, PMO Primary Safety Set)

Site	Observed Events[a]	Expected Events[b]	SIR	95% CI of SIR
All Sites	192	190.63	1.01	(0.87, 1.16)
Breast	35	50.15	0.70	(0.49, 0.97)
Colon Excluding Rectum	12	19.19	0.63	(0.32, 1.09)
Corpus And Uterus, Nos	5	9.94	0.50	(0.16, 1.17)
Digestive System	35	40.26	0.87	(0.61, 1.21)
Female Genital System	21	18.70	1.12	(0.70, 1.72)
Ovary	9	5.79	1.55	(0.71, 2.95)
Pancreas	8	6.05	1.32	(0.57, 2.60)
Stomach	7	2.54	2.76	(1.11, 5.68)
Thyroid	2	1.96	1.02	(0.12, 3.68)

Summary Characteristics of Subject Incident SAEs of Cellulitis/Erysipelas

	Placebo N = 6	Denosumab N = 17
Mean (SD) age in years	79 (10)	74 (8)
Mean (SD) onset from last dose in days	135 (43)	116 (97)
Median hospitalization in days	4	5
Event severity, n (%)		
Mild	0 (0)	1 (6)
Moderate	3 (50)	7 (41)
Severe	3 (50)	7 (41)
Life-threatening	0 (0)	1 (6)
Fatal	0 (0)	1 (6)
Lower extremity infection, n (%)	6 (100)	15 (88)
History venous stasis, varicose ulcers, other risks, n (%)	3 (50)	9 (53)
Received intravenous antibiotics, n (%)	5 (83)	14 (82)
Discontinued due to SAE, n (%)	0 (0)	0 (0)
Recurrent SAEs of cellulitis, n (%)	1 (17)	1 (6)

Clinical Symptoms of Serious Cellulitis/Erysipelas in 216 Study (13 subjects)

Clinical Sign or Symptom	Number of Patients with Cellulitis/ Erysipelas (N=13) n (%)
Fever	2 (15%)
Pain	6 (46%)
Erythema	7 (54%)
Swelling	6 (46%)
Warmth	4 (31%)
Regional adenopathy	2 (15%)

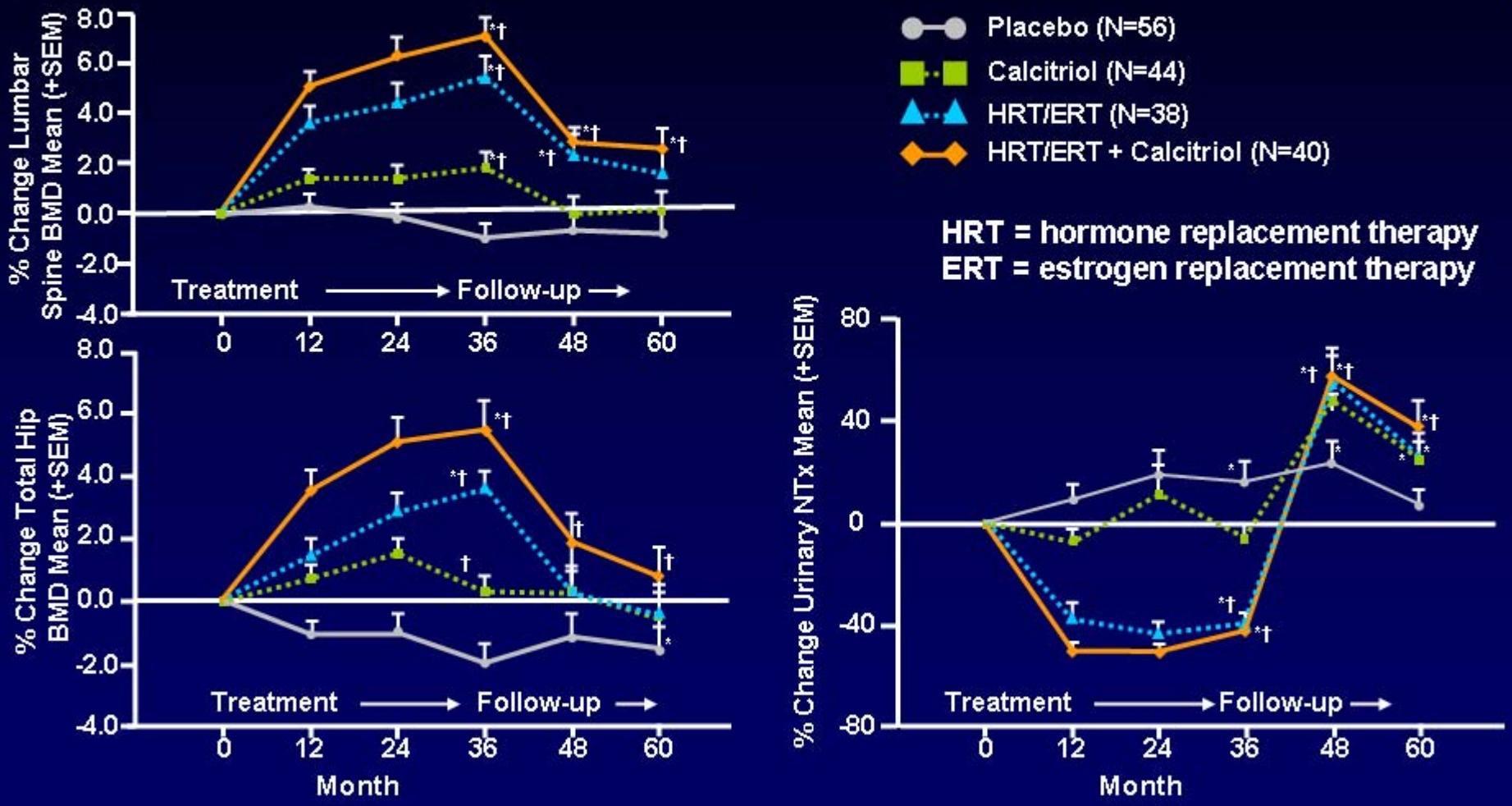
20030216: Incidence of Fracture after IP Discontinuation *7-month Minimum Follow-up*

	Placebo (N=3906)	Denosumab (N=3902)
Number of subjects	794	633
Total years of observation	525.6	397.3
Number of fractures	65	37
Vertebral fractures	40	23
Nonvertebral fractures	25	14
Fracture rate / 100 years	**12.4**	**9.3**

Study 20040135: Bisphosphonate Use For Subjects Who Never Fractured and Subjects Who Were Taking Bisphosphonates Prior to Their First Fracture During the Safety Follow-up Phase

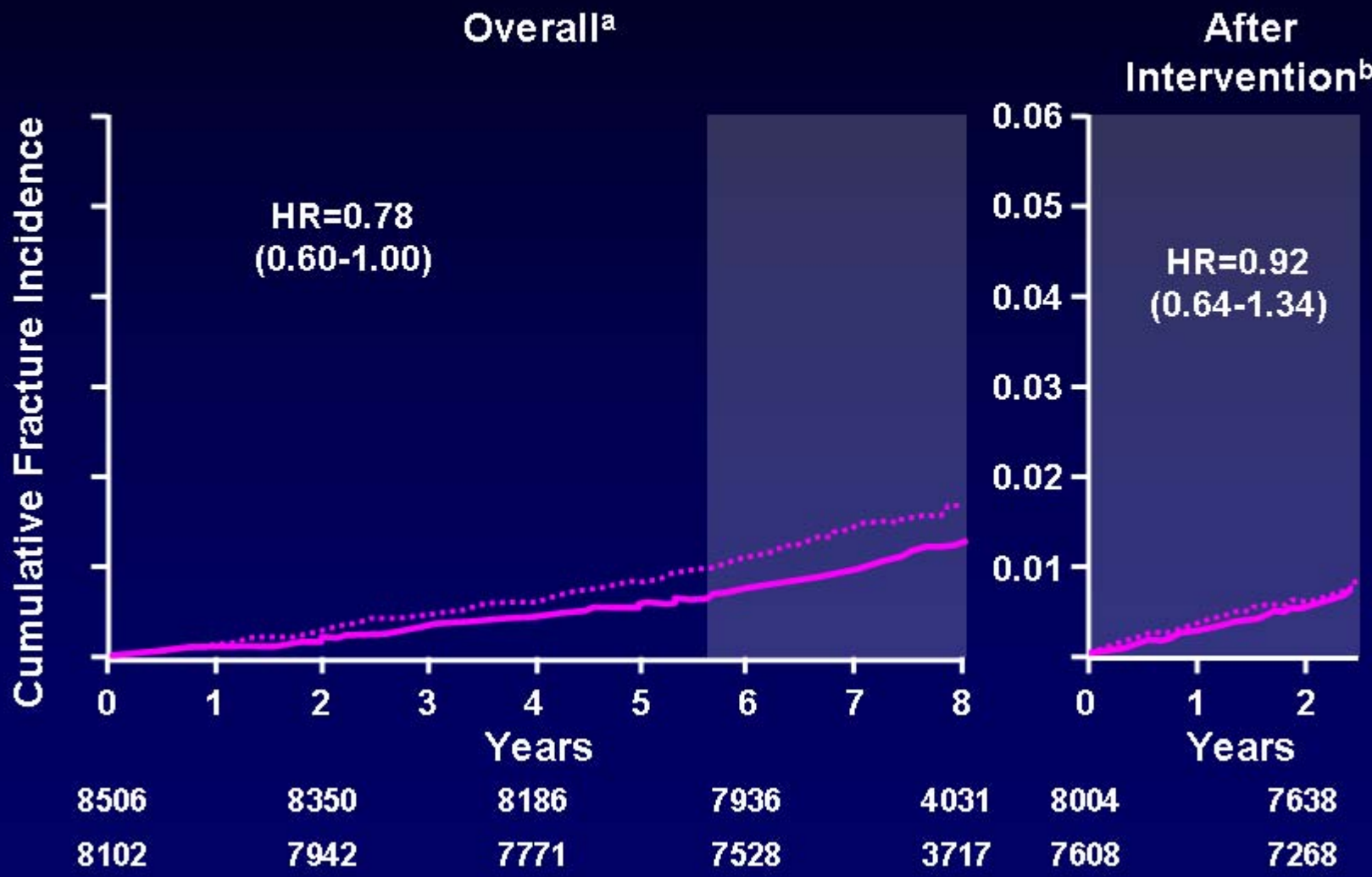
Preferred Term	Placebo (N=89) n (%)	Denosumab 60 mg Q6M (N=96) n (%)
Number of subjects reporting use of Bisphosphonates who never had a fracture or before their first fracture in safety follow-up phase	**20 (22.5)**	**11 (11.5)**
Alendronate Sodium	5 (5.6)	5 (5.2)
Ibandronate Sodium	10 (11.2)	3 (3.1)
Zoledronic Acid	4 (4.5)	2 (2.1)
Risedronate Sodium	4 (4.5)	1 (1.0)

Increased in Bone Turnover Markers and Decreases in BMD Have Been Observed with HRT Discontinuation



*P < 0.05 compared with baseline measurement
†P< 0.05 compared with placebo group
Adapted from Gallagher JC et al. *J Endocrinol Metab 2002*; 87(11): 4914-4923.

Risk for Hip Fracture in WHI Treatment and Withdrawal from Therapy



Adapted from Heiss G et al., JAMA 2008; 299 (9): 1036-1045.

Endocarditis SAEs (3 Denosumab, 2 Placebo)

- 2 serious endocarditis events occurred on placebo in Study 20040138
- 3 subjects in denosumab group in Study 20030216 reported serious events of endocarditis
  - Causative pathogen was not identified in any case
  - Diagnosis made clinically (e.g. echocardiography) in 3 cases
  - Cardiac valve vegetation pathologically verified in just 1 case

Study 20030216: Disease Characteristics in Subjects Who Discontinue Due to Breast Cancer

	New Diagnosis		Recurrence	
	Placebo	Denosumab 60 mg Q6M	Placebo	Denosumab 60 mg Q6M
Number of subjects with treatment emergent breast cancer	10 / 26	16 / 28	1 / 2	5 / 6
Timing of breast cancer event				
First month	0 / 2	1 / 2	0 / 0	2 / 2
Month 1 - Year 1	4 / 6	3 / 5	0 / 1	0 / 1
Year 1 - 2	4 / 10	6 / 8	1 / 1	2 / 2
Year 2 - 3	2 / 8	6 / 13	0 / 0	1 / 1
Stage at on-study diagnosis				
0, I, or II	7 / 16	9 / 19	NA	NA
III or IV	1 / 4	5 / 5	NA	NA
Unknown	2 / 6	2 / 4	NA	NA
Histology				
In situ	0 / 0	2 / 3	0 / 0	0 / 1
Invasive	8 / 22	14 / 23	1 / 2	3 / 3
Unknown	2 / 4	0 / 2	0 / 0	2 / 2

numerators: Number of subjects who discontinued from investigational product or study due to breast cancer

Cataract and Cataract Surgery in Elderly Males: High Prevalence and Incidence

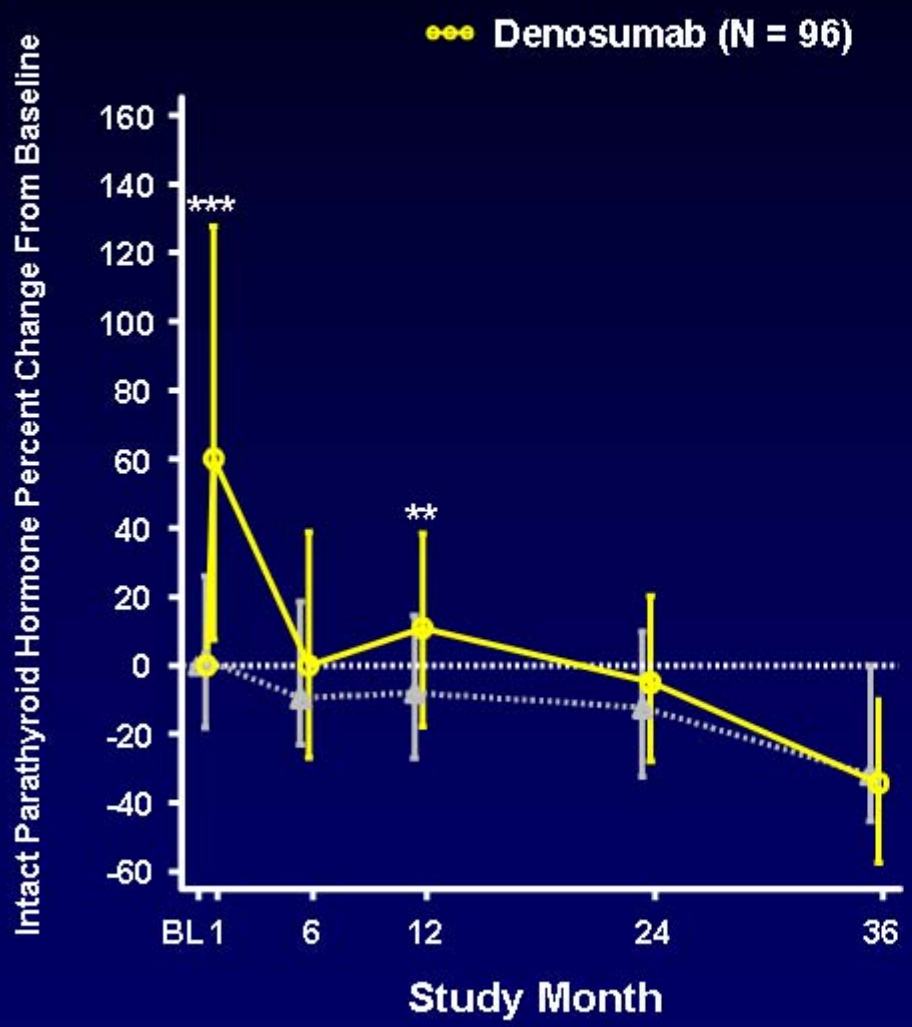
- Prevalent cataract by slit-lamp examination:
  - 47% - 71% in males ≥ 75 years[1]
- Incident cataract by slit-lamp examination:
  - 70% in males ≥75 years over 5-year period[2]
- Cataract surgery (US):
  - 7 to 8% of elderly males over 5-year period[2]

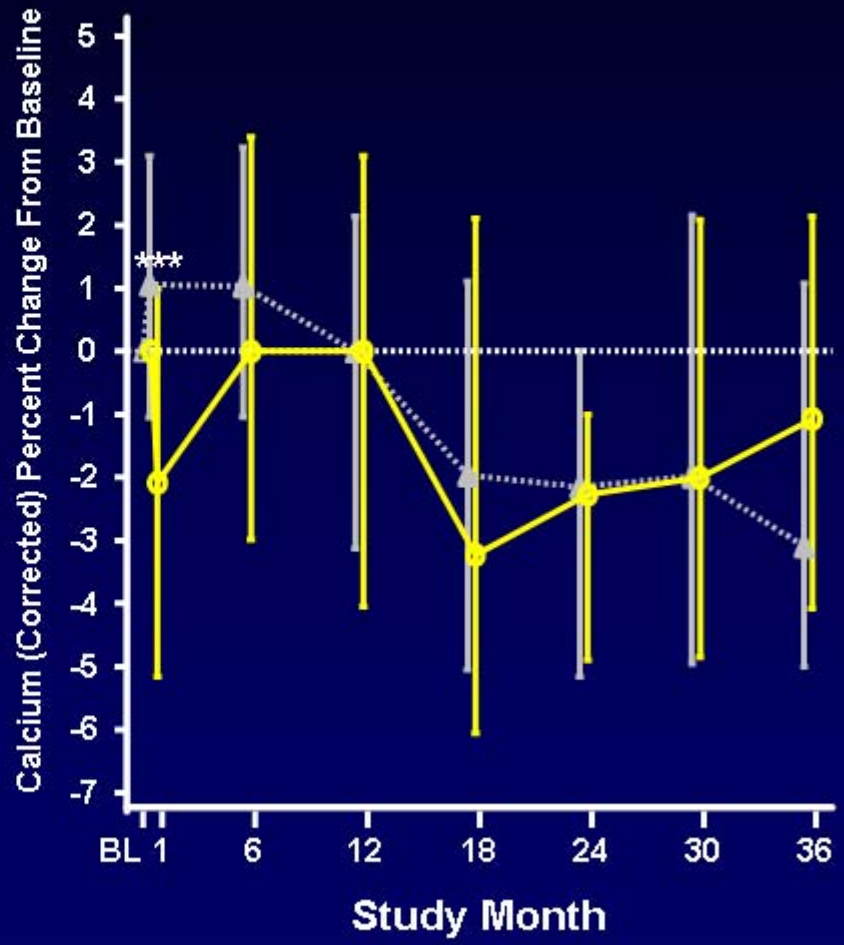
[1]The Eye Diseases Prevalence Research Arch Ophthalmol. 2004;122:487-94.
[2]Klein et al., Opthalmology 2002; 109 (11): 2052 - 7

Study 20030216: Geographic Regions

Region	N (%)
Western Europe	3534 (44.9)
Eastern Europe	2729 (34.7)
Latin America	934 (11.9)
North America	579 (7.4)
Australia/New Zealand	92 (1.2)

Study 216: Compensatory Increases in iPTH Observed are Consistent with Decreases in Serum Calcium



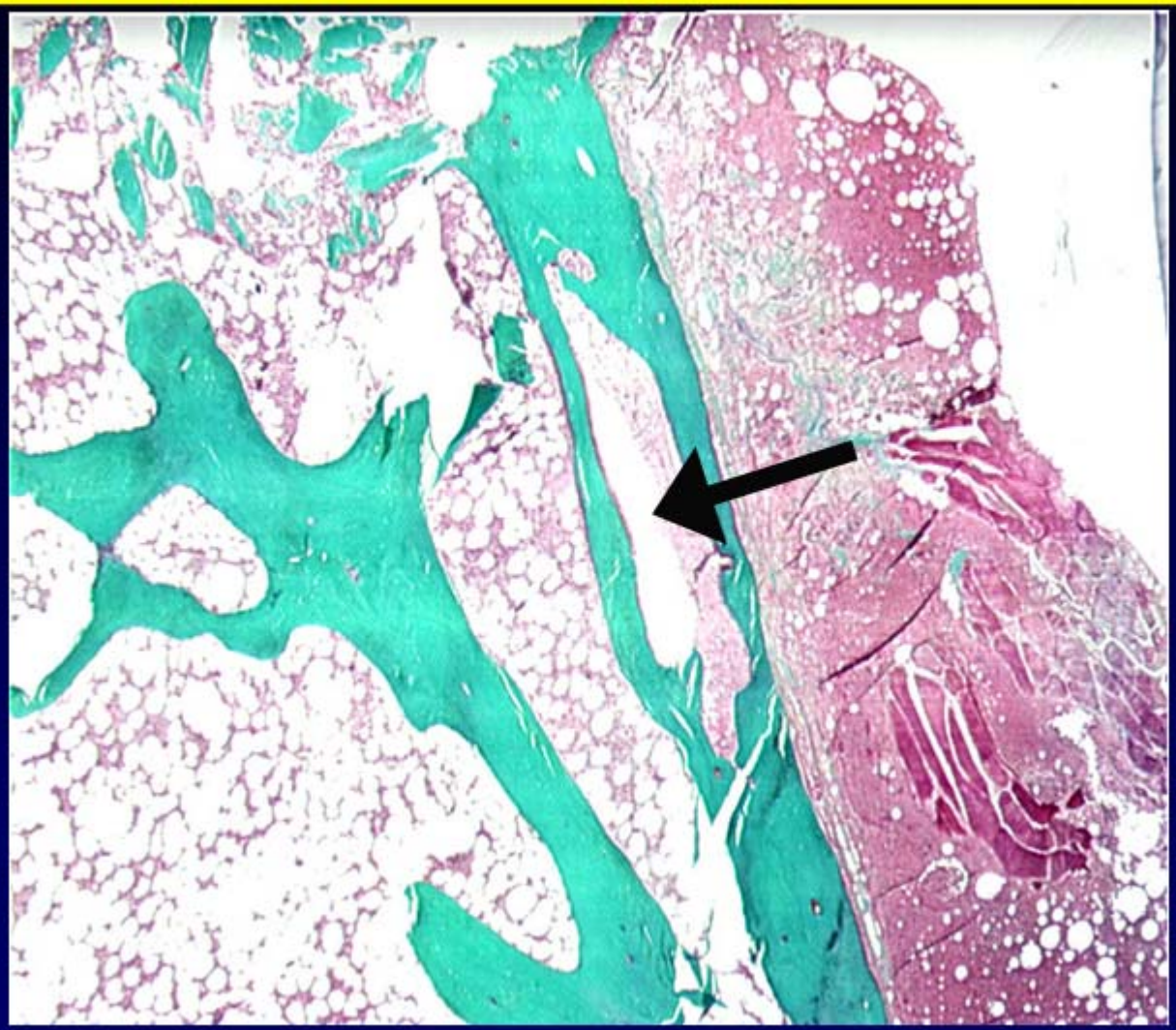


N = Number of randomized subjects enrolled in the bone marker substudy
* statistically significant (p-value ≤ 0.05); ** statistically significant (p-value ≤ 0.025);
*** statistically significant (p-value ≤ 0.01)

216 Study: Incidence of Hypocalcemia by Level of Renal Function

	15 - <30 ml/min		30 - <60 ml/min		60 - <90 ml/min		≥ 90 ml/min	
	Placebo (N=37) n (%)	Denosumab (N=36) n (%)	Placebo (N=1392) n (%)	Denosumab (N=1410) n (%)	Placebo (N=2034) n (%)	Denosumab (N=2015) n (%)	Placebo (N=410) n (%)	Denosumab (N=423) n (%)
<LLN – 8.0 mg/dl	0 (0.0)	0 (0.0)	7 (0.5)	22 (1.6)	2 (<0.1)	28 (1.4)	1 (0.2)	9 (2.1)
<8.0 – 7.5 mg/dl	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
<7.5 mg/dl	1 (2.7)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)

Subject 6613015
Top Right Cortex, 36M

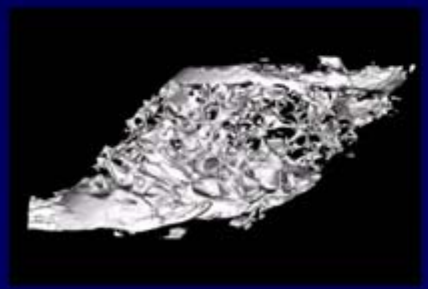


Subject 6613015: MicroCT Images of Bone Biopsies From

Month 24

2-Dimensional

3-Dimensional



MicroCT Data:

BVF: 9.7%

Trab No: 0.91/mm

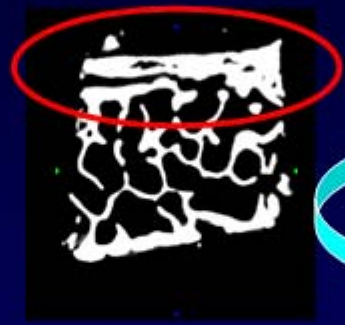
Trab Conn: 2.46/mm^3

Cort Th: 0.69, 0.67 mm

Cort Por: 2.96, 5.35%

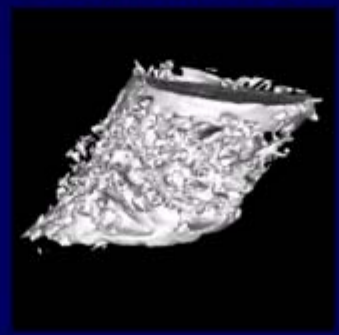
Month 36

2-Dimensional



Rotated 90°

3-Dimensional



MicroCT Data:

BVF: 27.2%

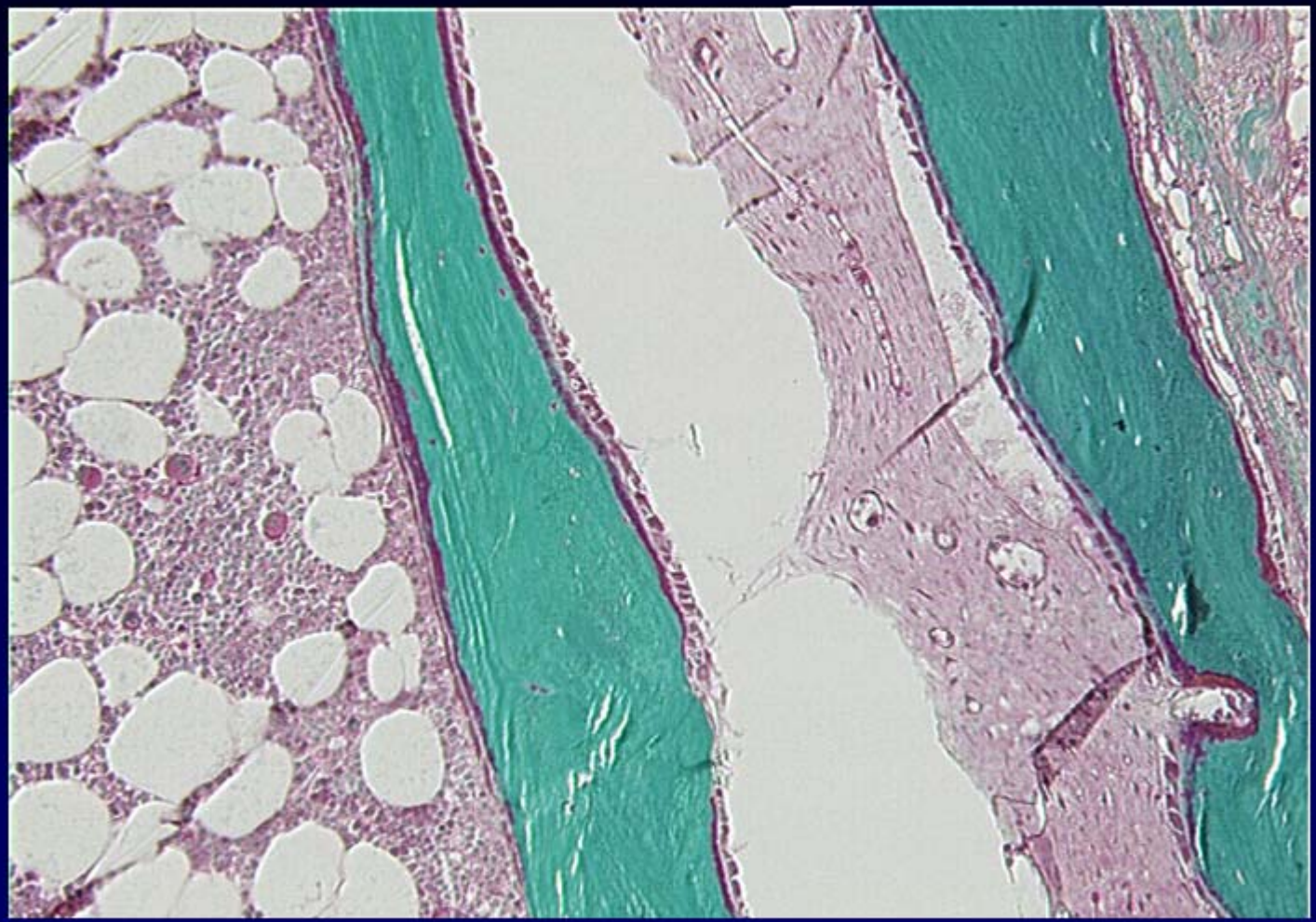
Trab No: 1.55/mm

Trab Conn: 2.70/mm^3

Cort Th: 0.70, 0.42 mm

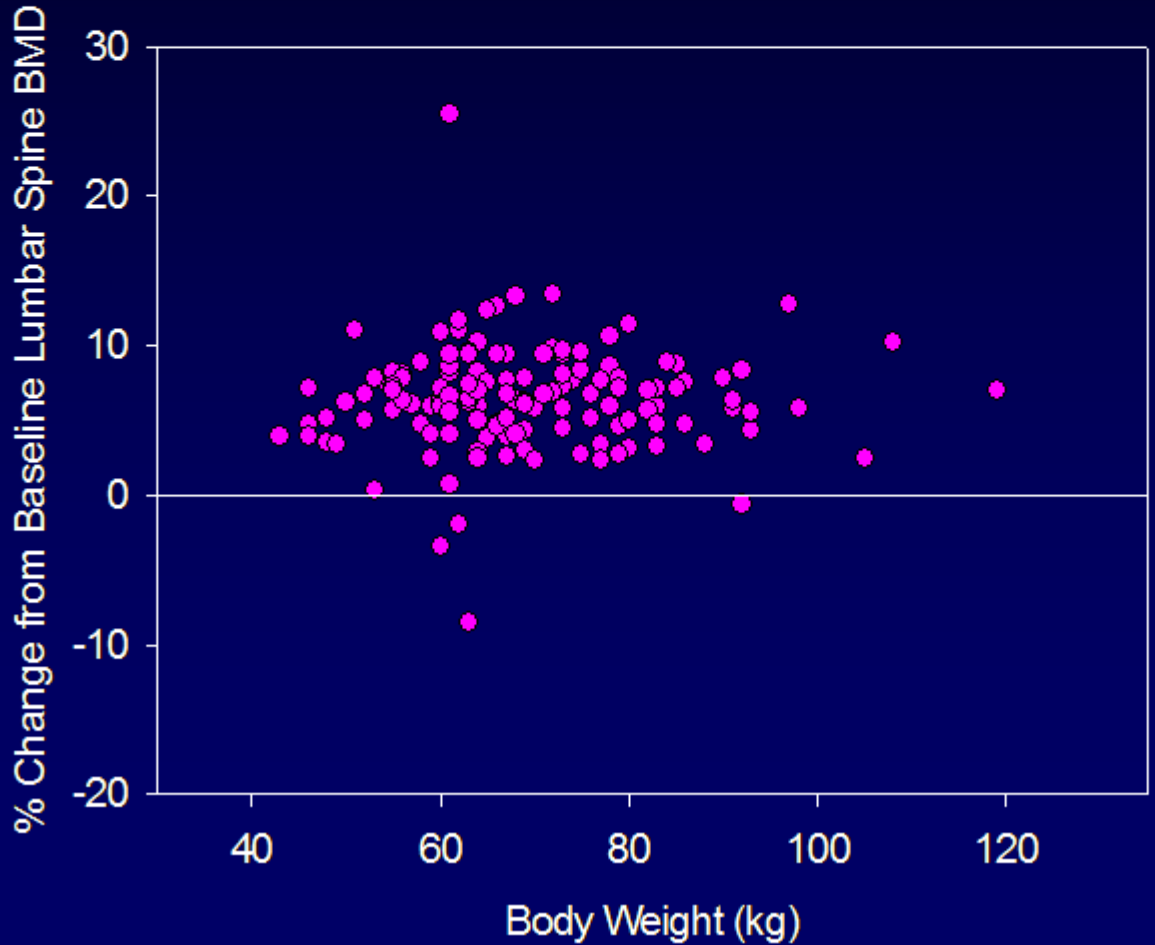
Cort Por: 2.83, 4.97%

Subject 6613015, M36
Cellularity at Periosteum

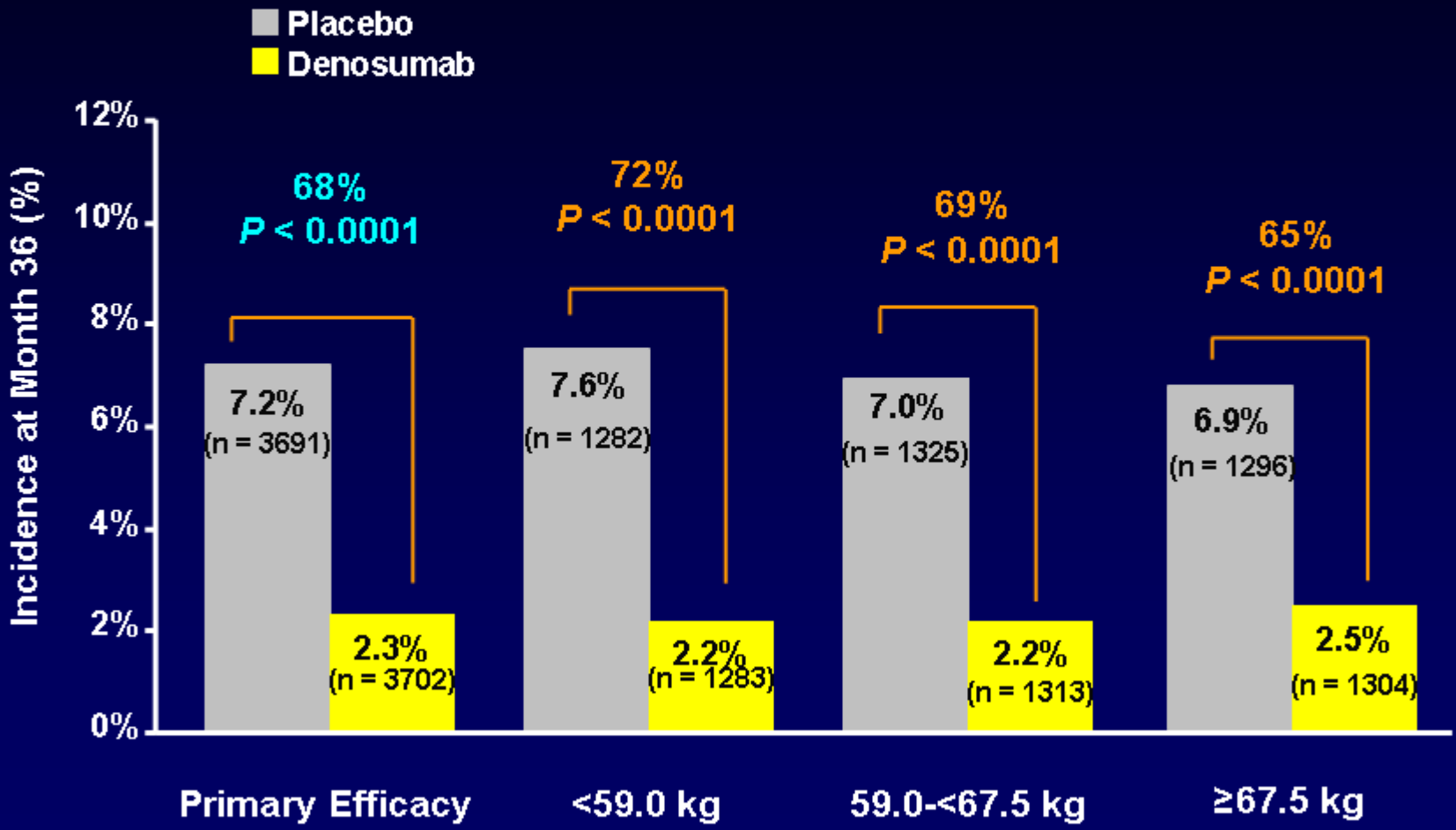


Body Weight Does Not Impact Individual BMD Response in Postmenopausal Women (60 mg Q6M)

%Change from Baseline in Lumbar Spine BMD (Month 24) vs. Body Weight in Postmenopausal Women (Study 20040132; 60 mg Q6M)

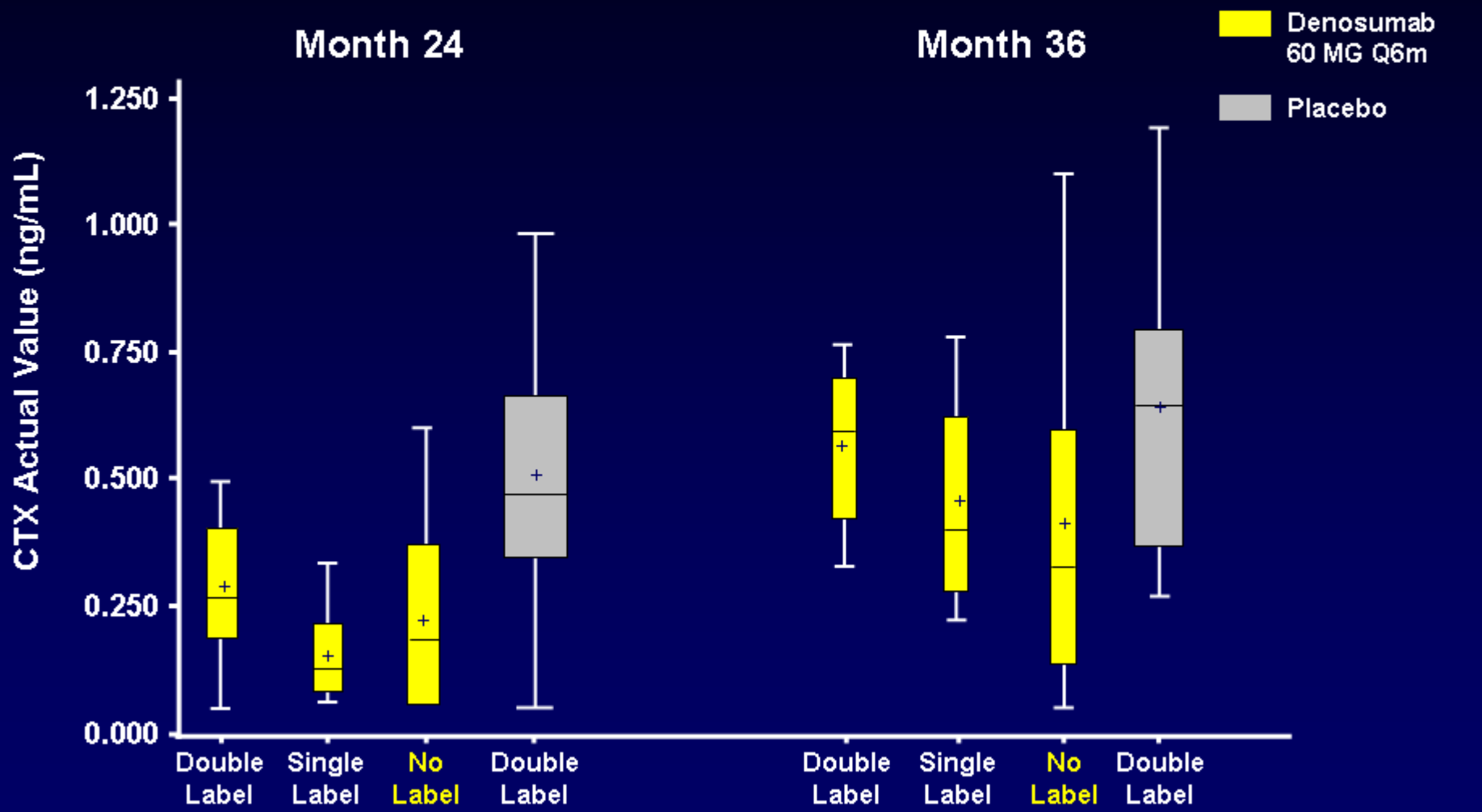


Study 20030216: New Vertebral Fracture Over 3 Years: By Baseline Body Weight Tertiles



Treatment-by-subgroup interaction p-value: 0.7796

Study 20030216:
CTx Value at Month 24 and 36 by Label Status



Aggregated Events of Serious Diverticulitis and its Complications were Relatively Balanced Between Treatment Groups

	PMO		HALT		Overall	
	Placebo (N=4041) n (%)	Denosumab 60 mg Q6M (N=4050) n (%)	Placebo (N=845) n (%)	Denosumab 60 mg Q6M (N=860) n (%)	Placebo (N=4886) n (%)	Denosumab 60 mg Q6M (N=4910) n (%)
Aggregate Diverticulitis *	**8 (0.2)**	**12 (0.3)**	**3 (0.4)**	**6 (0.7)**	**11 (0.2)**	**18 (0.4)**
Diverticulitis	6 (0.1)	10 (0.2)	0 (0.0)	6 (0.7)	6 (0.1)	16 (0.3)
Diverticulum	1 (<0.1)	2 (<0.1)	1 (0.1)	0 (0.0)	2 (<0.1)	2 (<0.1)
Diverticulum intestinal	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Enterovesical fistula	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (<0.1)	0 (0.0)

- **Clinical review of diverticular-related SAEs showed 3 subjects in placebo group reported SAEs of diverticulitis complications:**
  - 1 autopsy report of purulent diverticulitis
  - 2 reports of enterovesical fistula requiring surgical repair and antibiotics

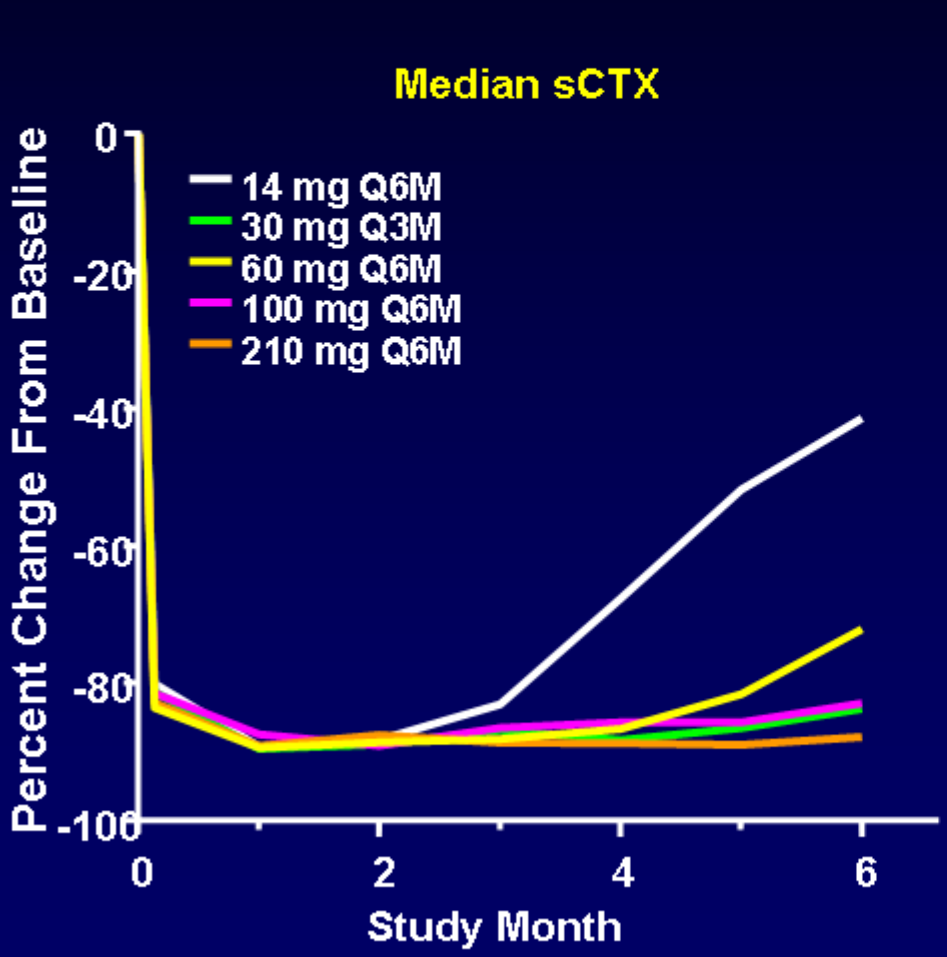
* Aggregate Diverticulitis includes terms that revealed an underlying etiology of diverticulitis with manual case review

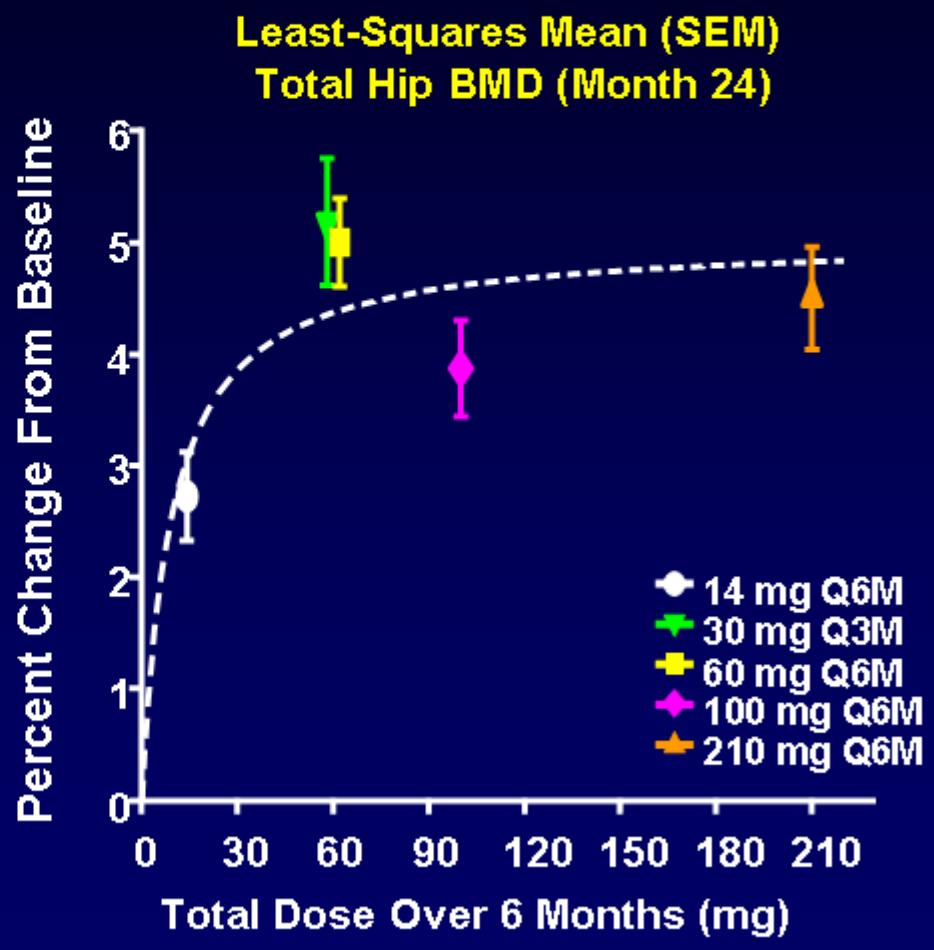
Table 18. Serious Adverse Events With Incidence ≥ 0.5% in Either Overall Group in the Primary PMO Safety Analysis Set, by Preferred Term in Descending Order of Frequency

	Study 20040132		Study 20030216		Overall	
Preferred Term	Placebo (N=165) n (%)	Denosumab 60 mg Q6M (N=164) n (%)	Placebo (N=3876) n (%)	Denosumab 60 mg Q6M (N=3886) n (%)	Placebo (N=4041) n (%)	Denosumab 60 mg Q6M (N=4050) n (%)
Number of subjects reporting SAEs [a]	9 (5.5)	19 (11.6)	972 (25.1)	1004 (25.8)	981 (24.3)	1023 (25.3)
Osteoarthritis	0 (0.0)	3 (1.8)	79 (2.0)	63 (1.6)	79 (2.0)	66 (1.6)
Pneumonia	0 (0.0)	3 (1.8)	36 (0.9)	34 (0.9)	36 (0.9)	37 (0.9)
Atrial fibrillation	0 (0.0)	0 (0.0)	33 (0.9)	36 (0.9)	33 (0.8)	36 (0.9)
Breast cancer	0 (0.0)	0 (0.0)	25 (0.6)	34 (0.9)	25 (0.6)	34 (0.8)
Angina pectoris	0 (0.0)	0 (0.0)	18 (0.5)	33 (0.8)	18 (0.4)	33 (0.8)
Cerebrovascular accident	0 (0.0)	0 (0.0)	23 (0.6)	32 (0.8)	23 (0.6)	32 (0.8)
Myocardial infarction	0 (0.0)	0 (0.0)	23 (0.6)	25 (0.6)	23 (0.6)	25 (0.6)
Radius fracture	0 (0.0)	0 (0.0)	23 (0.6)	25 (0.6)	23 (0.6)	25 (0.6)
Cataract	0 (0.0)	0 (0.0)	28 (0.7)	21 (0.5)	28 (0.7)	21 (0.5)
Back pain	0 (0.0)	0 (0.0)	20 (0.5)	20 (0.5)	20 (0.5)	20 (0.5)
Hypertension	0 (0.0)	0 (0.0)	22 (0.6)	19 (0.5)	22 (0.5)	19 (0.5)
Femur fracture	0 (0.0)	0 (0.0)	28 (0.7)	14 (0.4)	28 (0.7)	14 (0.3)
Femoral neck fracture	0 (0.0)	0 (0.0)	20 (0.5)	13 (0.3)	20 (0.5)	13 (0.3)

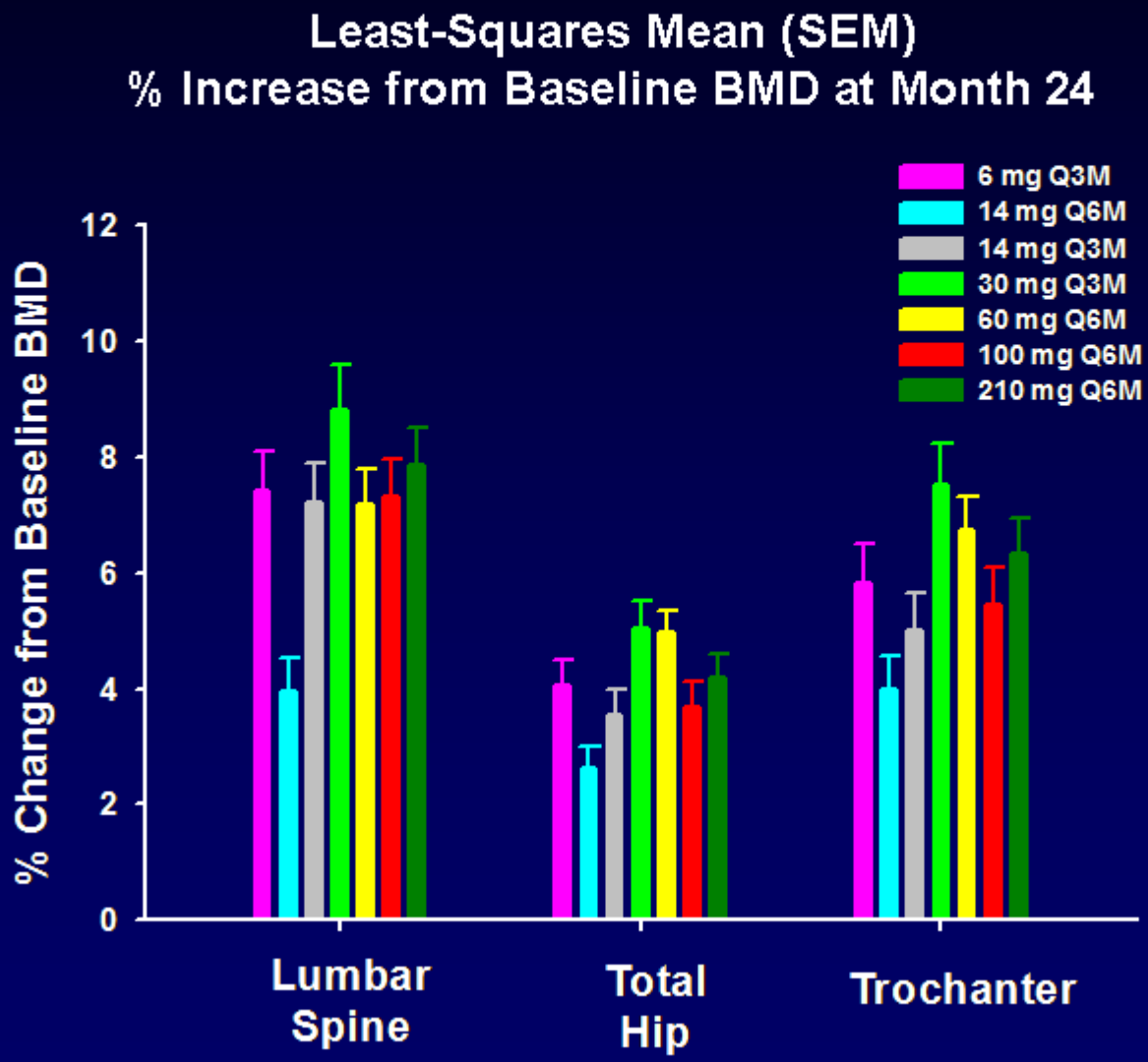
N = Number of subjects who received ≥1 dose of investigational product
n = Number of subjects reporting ≥1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 11.0.
[a] "Number of subjects reporting SAEs" includes all SAEs, regardless of incidence.
Source: Integrated Analysis of Safety (IAS)

Phase 2 Study 20010223: The Denosumab 60 mg Dose was the Lowest Q6M Regimen Evaluated that Provided Maximal Gains in BMD

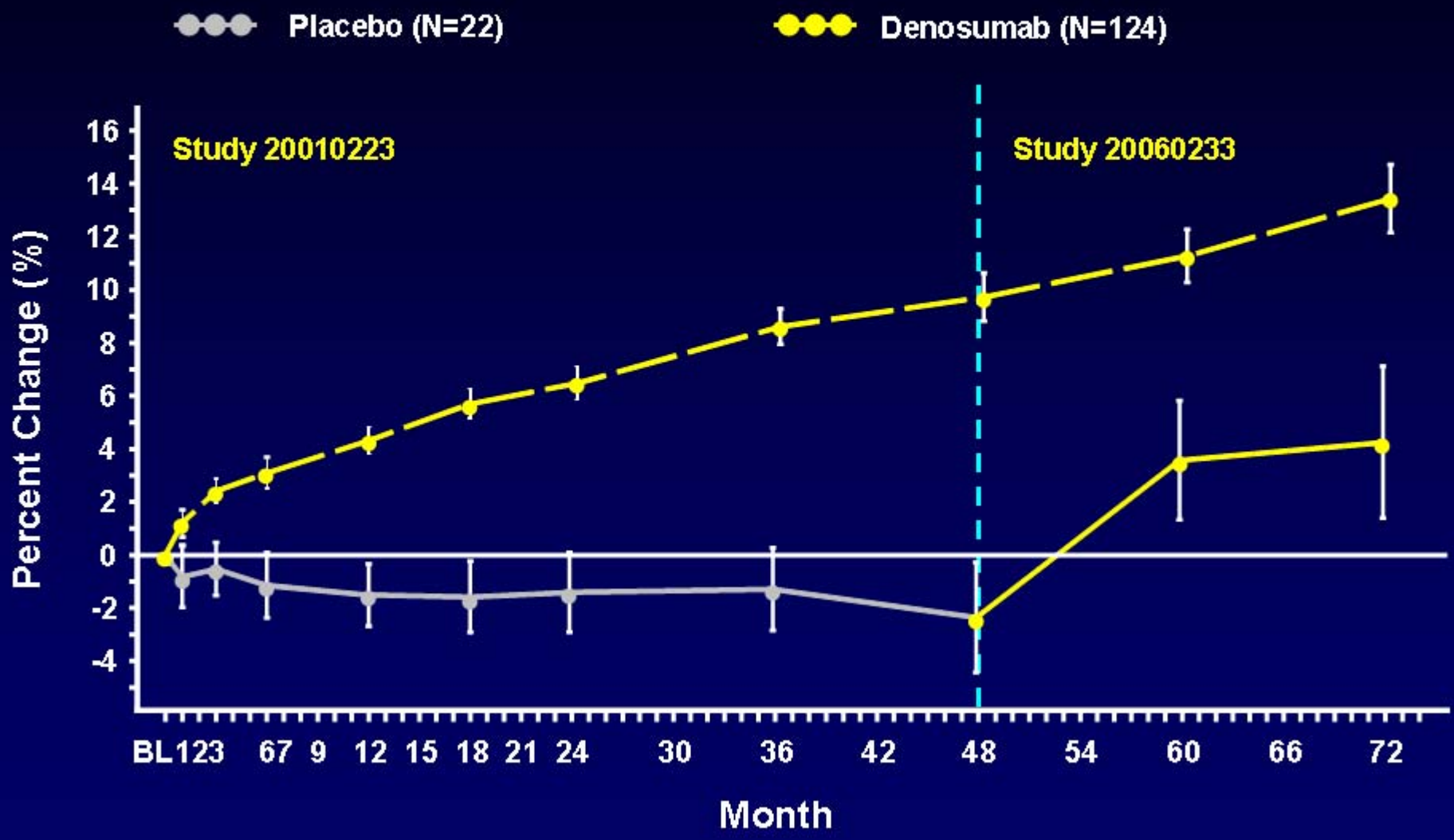




Month 24 BMD Data from the Phase 2 Dose-Ranging Study (20010223)



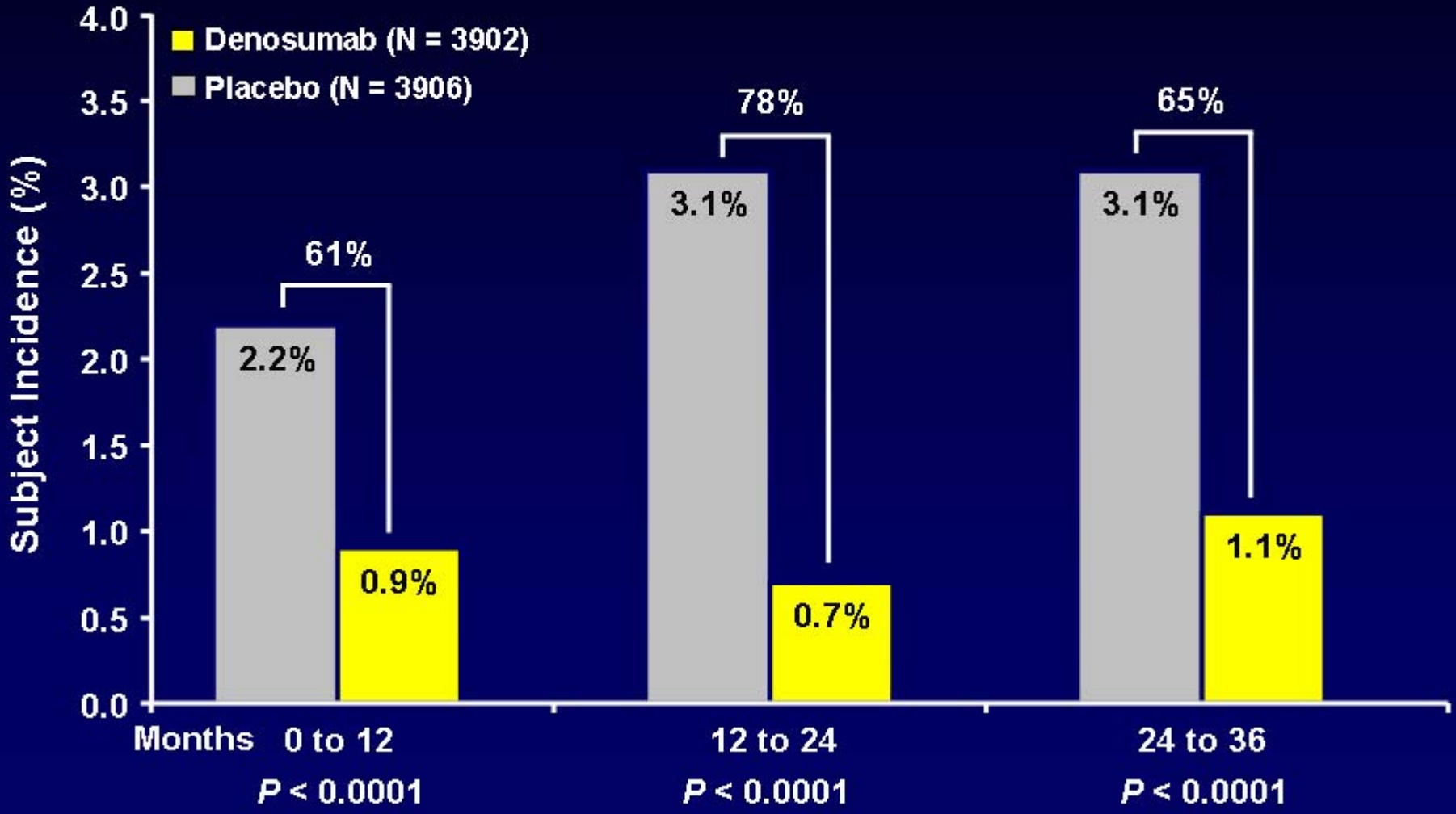
Increases in BMD Through Six Years of Continuous Denosumab Treatment: Lumbar Spine



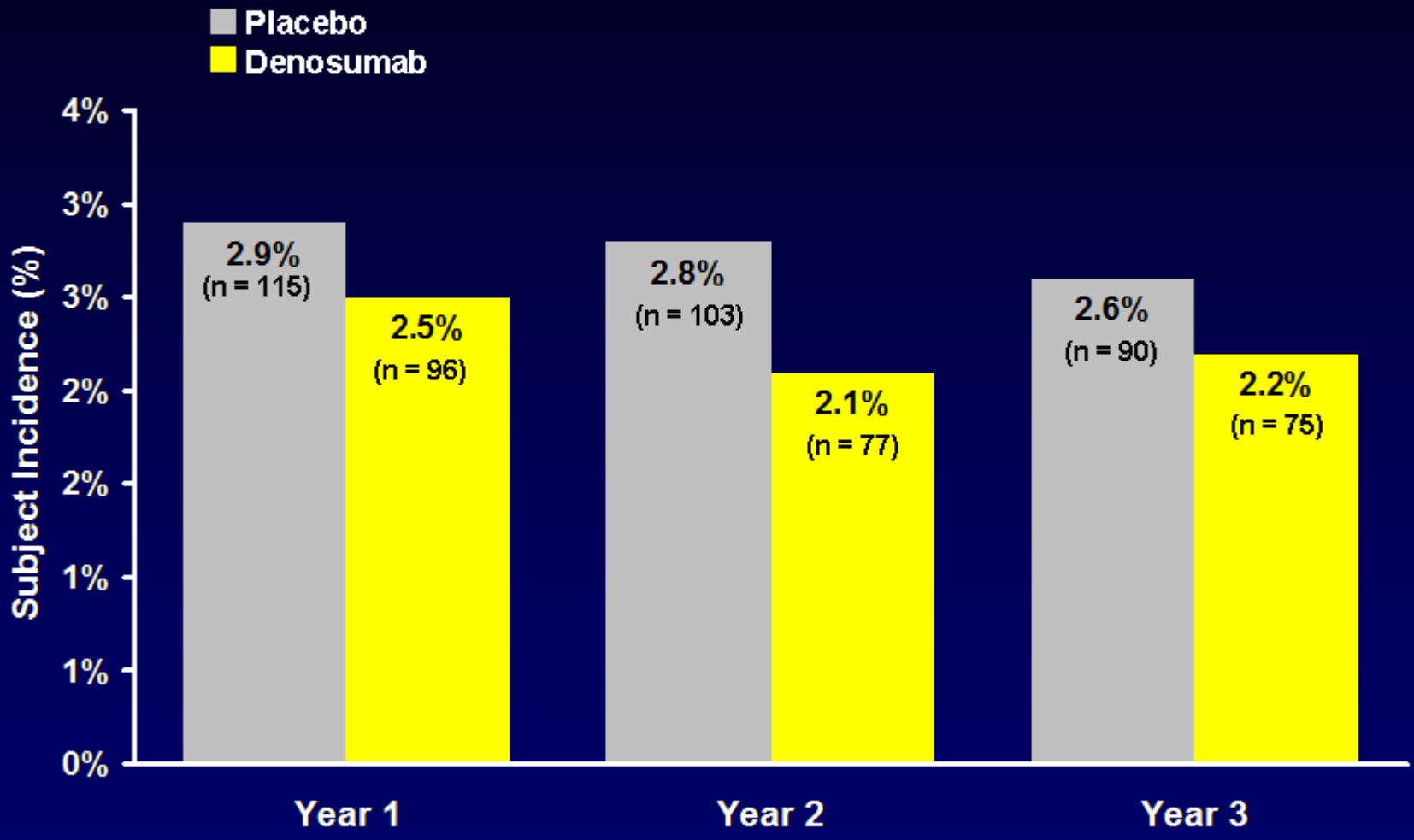
Number Needed to Treat

- Primary efficacy analysis
  - New vertebral fracture NNT=21
  - Nonvertebral fracture NNT=68
  - Hip fracture NNT=205
- High-risk group
  - New vertebral fracture NNT=11
  - Nonvertebral fracture NNT=25
  - Hip fracture NNT=71

PMO Fracture Study – 20030216: Denosumab Reduced New Vertebral Fracture Risk Year by Year



Study 20030216: Denosumab Reduced Non-vertebral Fracture Risk Year by Year

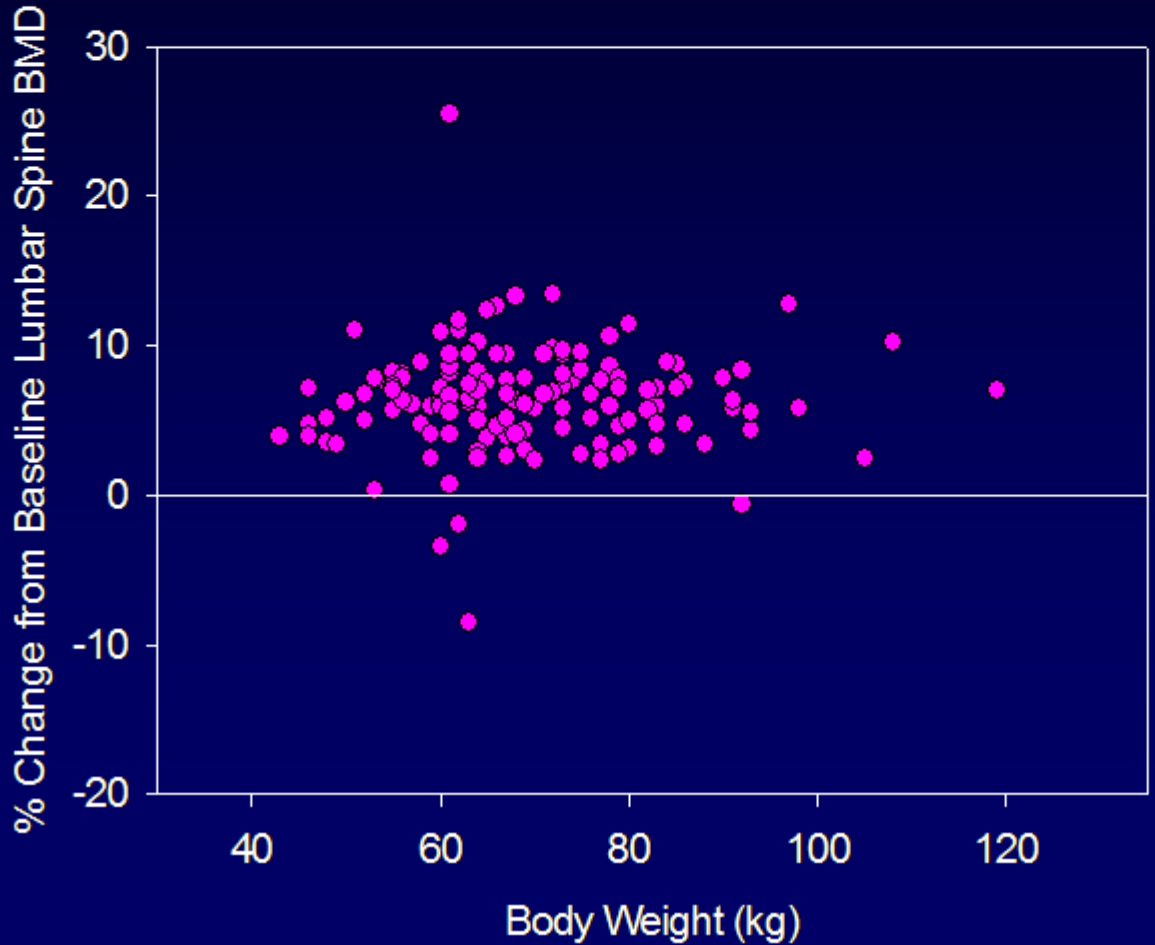


Study 20030216: Fractures on Study Year by Year

	Year 1 n (%)	Year 2 n (%)	Year 3 n (%)
New Vertebral fracture			
Placebo	82 (2.2)	107 (3.1)	98 (3.1)
Denosumab	32 (0.9)	24 (0.7)	35 (1.1)
Non-verterbral fracture			
Placebo	115 (2.9)	103 (2.8)	90 (2.6)
Denosumab	96 (2.5)	77 (2.1)	75 (2.2)
Hip fracture			
Placebo	20 (0.5)	14 (0.4)	9 (0.3)
Denosumab	10 (0.3)	4 (0.1)	12 (0.3)
Major osteoporotic fracture			
Placebo	105 (2.7)	117 (3.2)	81 (2.3)
Denosumab	81 (2.1)	59 (1.6)	62 (1.8)
Clinical verterbral fracture			
Placebo	28 (0.7)	39 (1.1)	26 (0.8)
Denosumabs	10 (0.3)	9 (0.2)	12 (0.3)

Body Weight Does Not Impact Individual BMD Response in Postmenopausal Women (60 mg Q6M)

%Change from Baseline in Lumbar Spine BMD (Month 24) vs. Body Weight in Postmenopausal Women (Study 20040132; 60 mg Q6M)



No Difference in BMD Effect by Weight/BMI

- Increases from baseline to month 36 in total hip BMD in body weight subgroups (< 55; 55 to < 65; 65 to < 75; and ≥ 75 kg) were similar among denosumab-treated subjects within those subgroups (4.9%, 5.2%, 5.0%, and 4.8%, respectively)
- As expected, and consistent with observations in other studies, subjects treated with placebo who weighed more did not lose BMD as rapidly (-1.8%, -1.5%, -1.2%, and -1.0%, respectively)
- Thus, the difference between the denosumab and placebo groups decreased with increasing body weight (6.7%, 6.6%, 6.1%, and 5.7%, respectively; no qualitative interaction was observed
- Within each body weight subgroup, denosumab increased lumbar spine BMD compared to placebo ($p < 0.0001$)
- Therefore, the greater difference in total hip BMD between the denosumab and placebo groups in subjects with lower body weight does not appear to be clinically relevant since the changes from baseline in the denosumab group were consistent in magnitude across weight subgroups
- Similar effects observed in BMI subgroups

Study 20040135:
AE of breast cancer progression (per clinical review)

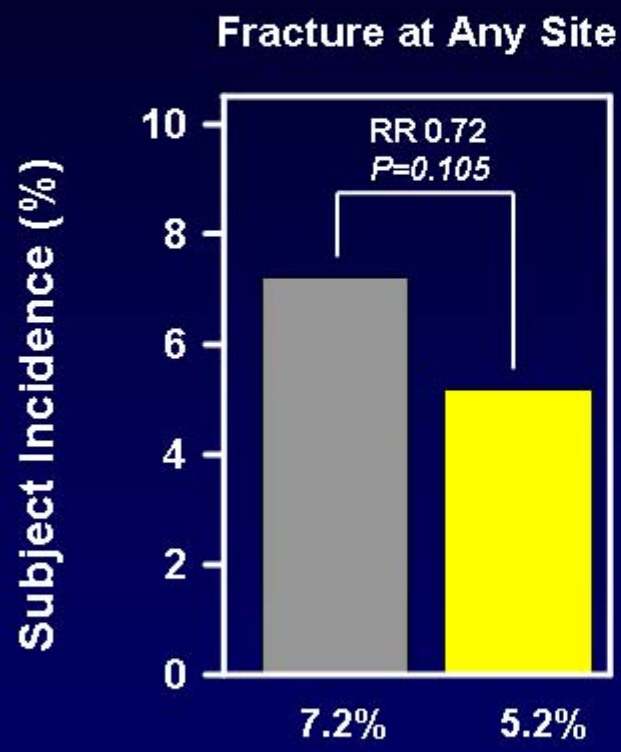
On treatment phase

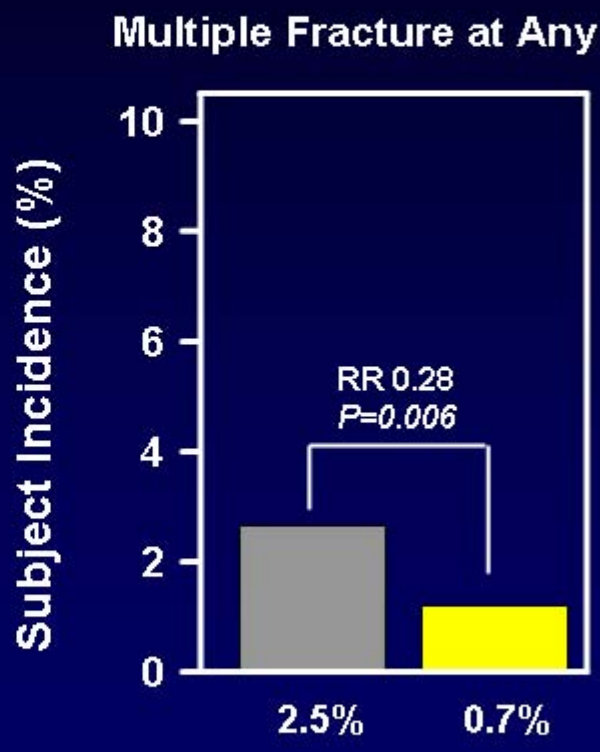
	Denosumab	Placebo
	N = 129	N = 120
Disease progression as AE	4 (3.1%)	3 (2.5%)

Off treatment phase (120 day followup)

	Denosumab	Placebo
	N = 93	N = 92
Disease progression as AE	2 (2.1%)	2 (2.2%)

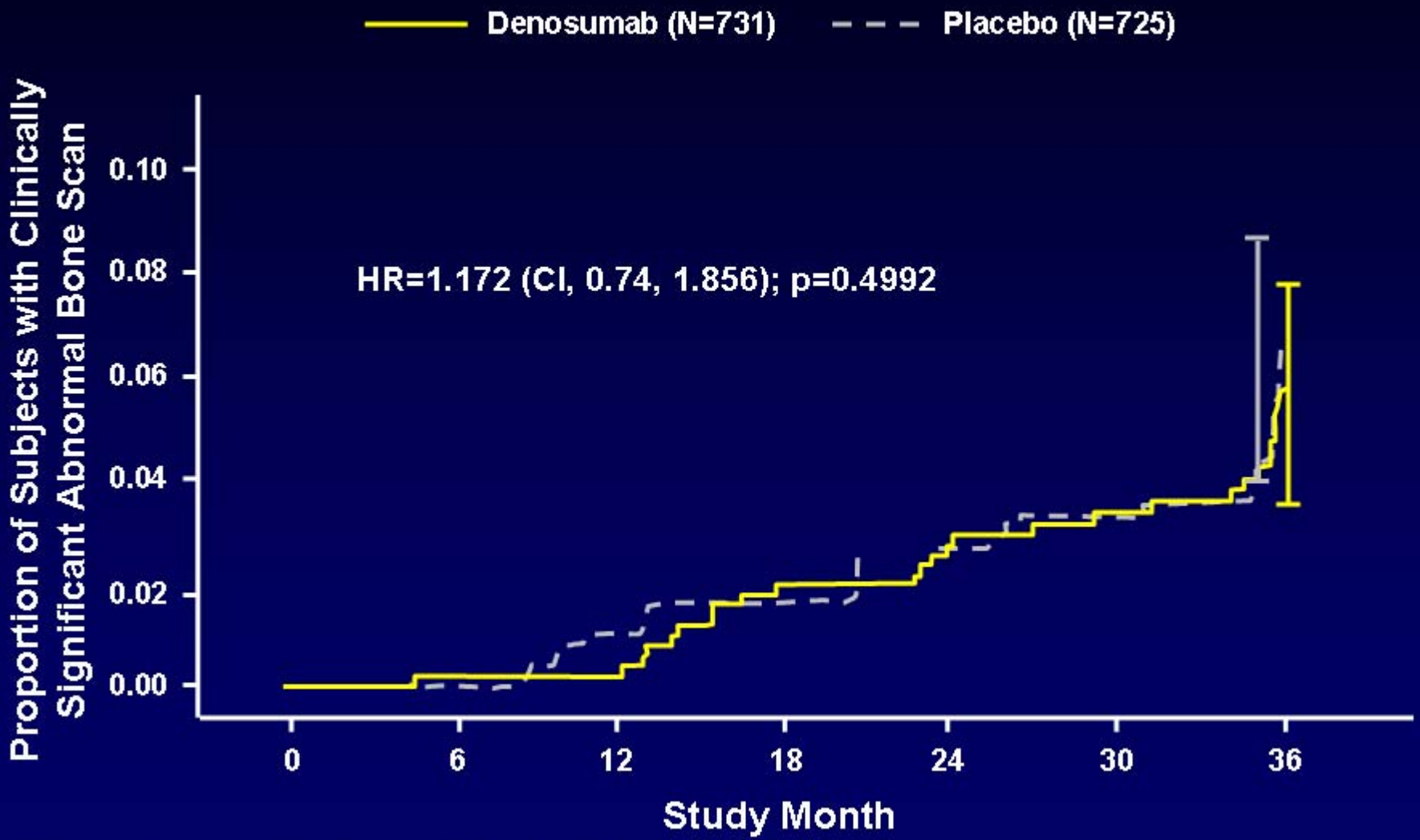
Study 20040138: Effect of Denosumab on Fracture at Any Site at 36 Months





Placebo (N=734) Denosumab (N=734)

Study 20040138: Denosumab Not Associated with Disease Progression End-of-study Bone Scan



N=Number of subjects who received ≥1 dose of investigational product